Interaction of vascular smooth muscle cells and endothelial cells in atherosclerosis on the background of metabolic syndrome

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The objective: was to determine the interaction of vascular smooth muscle cells with endothelial cells in the process of atherogenesis in the presence of metabolic syndrome.

Materials and methods. We studied the following groups: Group I – 50 patients who died as a result of complications associated with cerebral atherosclerosis in the setting of metabolic syndrome, Group II – 50 patients who died as a result of complications associated with cerebral atherosclerosis without a history metabolic syndrome and Group III (comparison group) – 50 patients who died from causes unrelated to MS and AS.

For the study we used the following histological and histochemical methods: hematoxylin-eosin, Masson's method, Van Gieson's method, Weigert's method, and immunohistochemical examination using monoclonal antibodies. For the identification of smooth muscle cells: immunocytochemical markers – Actin Smooth Muscle Ab-1 (Clone 1A4), Vimentin Ab-2 (Clone V9), Desmin (Muscle Cell Marker Ab-1 Clone D33), immunocompetent cells – CD4 (CD4 Ab-8), CD8 (SP-16), CD20 (CD20 Ab-1), CD68 (CD68/Macrophage Marker Ab-4) and to determine the endothelium state, immunocytochemical marker – CD31/PECAM-1 (Endothelial Cell Marker) Ab-1.

Results. In atherosclerotic lesions of cerebral arteries with metabolic syndrome manifestations, in the arterial wall media a significantly higher expression of desmin was observed in smooth muscle cells (SMCs) compared to other study groups. It should be noted that the migration of smooth muscle cells from the media and their intensive proliferation is directly dependent on endothelial and fibroblast factors. The immunohistochemical reaction with vimentin revealed the presence of connective tissue components and severe arterial wall fibrosis.

The expression of vimentin showed that vascular wall fibrosis increases with the progression of the underlying disease – metabolic syndrome. We observed migration and proliferation of SMCs, endocytosis, and synthesis of connective tissue components that actively contribute to intimae hypertrophy and atheromatous changes. As for the change in VSMCs phenotype, they demonstrate an extremely high degree of plasticity, and this affects the loss of expression of their contractile genes, including smooth muscle cell alpha-actin. We also noted potentiation of atherosclerotic changes resulted from formation of less differentiated forms of smooth muscle cells.

Atherogenesis can be initiated by both certain substances, such as cholesterol and lipoproteins, and endothelial changes – activated and damaged endothelium can participate in atherogenesis. Endothelial activation is also accompanied by the production of cell growth factors (Sitia S. et al., 2010). We observed monocyte adhesion to the arterial endothelium, the presence of monocytes under the endothelium their migration into the intimae with subsequent proliferation and formation of foam cells. This indicates their important role in the development of atherosclerosis by potentiating inflammation in the vascular wall and promoting the VSMCs phenotype transformation.

Conclusions. Changes in the phenotype of arterial intimae SMCs are accompanied by increased proliferation, and modified SMCs, with their high activity of synthesis of extracellular connective tissue components (elastin, collagen and glycosaminoglycans), are responsible for the formation of the plaques fibrous base. The presence of lymphocytes in the atherosclerotic process involves interaction with macrophages, endothelial cells and SMCs. A decrease in the number of endothelial progenitor cells, which are actively involved in the process of endothelial regeneration, contributes to the development of atherosclerosis.

Keywords: endothelium, endothelial cells, vascular smooth muscle cells, immunocompetent cells, metabolic syndrome, atherosclerosis.

Взаємодія гладком'язових клітин судин і ендотеліальних клітин при атеросклерозі на тлі метаболічного синдрому

Д. С. Маньковський, Н. Я. Чуйко

Мета дослідження: визначити взаємодію гладком'язових клітин (ГМК) судин з ендотеліальними клітинами у процесі атерогенезу за наявності метаболічного синдрому.

Матеріали та методи. Пацієнти склали наступні групи: I група – 50 пацієнтів, які померли внаслідок ускладнень церебрального атеросклерозу на тлі метаболічного синдрому, II група – 50 пацієнтів, які померли внаслідок ускладнень церебрального атеросклерозу, у яких не було діагностовано метаболічний синдром в анамнезі III група (група порівняння) – 50 пацієнтів, які померли від причин, не пов'язаних із метаболічним синдромом та атеросклерозом.

Для дослідження використовували наступні гістологічні та гістохімічні методи: гематоксилін-еозин, метод Массона, метод Ван Гісона, метод Вейгерта, імуногістохімічне дослідження з використанням моноклональних антитіл. Для іден-

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тифікації ГМК – імуноцитохімічні маркери – Actin Smooth Muscle Ab-1 (Clone 1A4), Vimentin Ab-2 (Clone V9), Desmin (Muscle Cell Marker Ab-1 Clone D33), імунокомпетентні клітини – CD4 (CD4 Ab). -8), CD8 (SP-16), CD20 (CD20 Ab-1), CD68 (CD68/маркер макрофагів Ab-4) та для визначення стану ендотелію імуноцитохімічний маркер – CD31/ PECAM-1 (маркер ендотеліальних клітин) Ab-1.

Результати. При атеросклеротичних ураженнях церебральних артерій за наявності ознак метаболічного синдрому в м'язовій оболонці артеріальної стінки спостерігалася достовірно більша експресія десміну в ГМК порівняно з іншими групами дослідження. Слід зазначити, що міграція ГМК із м'язової оболонки та їх інтенсивна проліферація безпосередньо залежать від ендотеліальних і фібробластних факторів. Імуногістохімічна реакція з віментином виявила наявність компонентів сполучної тканини та виражений фіброз артеріальної стінки.

Експресія віментину показала, що фіброз судинної стінки посилюється з прогресуванням основного захворювання – метаболічного синдрому. Ми відзначали міграцію та проліферацію ГМК, ендоцитоз та синтез компонентів сполучної тканини, які активно сприяють гіпертрофії інтими та атероматозним змінам. Що стосується зміни фенотипу VSMCs, то вони демонструють надзвичайно високий ступінь пластичності, що впливає на втрату експресії їхніх скоротливих генів, включаючи альфа-актин гладком'язових клітин. Також ми відзначали потенціювання атеросклеротичних змін унаслідок утворення менш диференційованих форм ГМК.

Атерогенез може бути ініційований як певними речовинами, такими як холестерин і ліпопротеїни, так і змінами ендотелію – в атерогенезі може брати участь активований і пошкоджений ендотелій. Активація ендотелію також супроводжується продукцією клітинних факторів росту (Sitia S. et al., 2010). Ми спостерігали адгезію моноцитів до ендотелію артерій, наявність моноцитів під ендотелієм, їхню міграцію в інтиму з подальшою проліферацією та утворенням пінистих клітин. Це вказує на їхню важливу роль у розвитку атеросклерозу шляхом потенціювання запалення в судинній стінці та сприяння трансформації фенотипу VSMC.

Висновки. Зміни фенотипу ГМК артеріальної інтими супроводжуються посиленою проліферацією, а модифіковані ГМК з високою активністю синтезу компонентів позаклітинної сполучної тканини (еластину, колагену та глікозаміногліканів) відповідають за формування фіброзної основи бляшок. Присутність лімфоцитів в атеросклеротичному процесі передбачає взаємодію з макрофагами, ендотеліальними клітинами та ГМК. Зменшення кількості ендотеліальних клітин-попередників, які беруть активну участь у процесі регенерації ендотелію, сприяє розвитку атеросклерозу.

Ключові слова: *ендотелій, ендотеліальні клітини, гладком'язові клітини судин, імунокомпетентні клітини, метаболічний синдром, атеросклероз.*

Today, the metabolic syndrome (MS) is one of the most important medical and social problems in the world and in Ukraine in particular. Ukraine is considered to be a country with a high risk of cardiovascular diseases. For several decades, mortality due to CVD has been ranked second in the structure of overall mortality. The main metabolic syndrome manifestations are disorders of carbohydrate and fat metabolism, as well as abnormalities in mechanisms of blood pressure regulation and endothelial function, the main cause of which is a decrease in tissue sensitivity to insulin.

It is believed that metabolic syndrome is a quite complicated but reversible condition [1, 2]. Its uniqueness lies in the fact that it is possible to reduce its manifestations by influencing one of the components, since there is often a cause-and-effect link between them. The main morphological substrate of arterial lesions in the metabolic syndrome is atherosclerosis (AS), the morphogenesis of which is currently under-investigated [4–6].

In recent years, the onset and development of AS has been considered in terms of monoclonal proliferation of smooth muscle cells (SMC) and changes in the endothelium. The endothelial barrier is believed to play an active role in atherosclerotic plaque development by regulating endothelial permeability and by local secretion of vasoactive mediators [5, 7, 20, 21]. While actively denying the role of mechanical endothelial damage, it is proposed to rely on changes in endothelial permeability and vascular wall cell proliferation [5].

Arterial smooth muscle cells comprise more than 90% of all atherosclerotic plaque cells and are present in the preatherosclerotic arterial intimae starting from the intrauterine period [10]. The identification of lipid-enriched smooth muscle cells (SMCs) in atherosclerotic vascular plaques raised initial questions about vascular cell identity and plasticity, i.e., modulation of cellular phenotype and function [10, 14]. However, there is uncertainty as to which cells in atherosclerotic lesions are derived from smooth muscle cells and which from macrophages, mainly due to the lack of clear studies regarding their origin [10, 11, 14].

Local infiltration by macrophages in atherosclerotic lesions areas is often combined with T-lymphocytes accumulation, indicating the inflammatory nature of the process [16, 19]. Subsequently, a number of studies have shown that in atherosclerotic vascular plaques were found smooth muscle cells actively expressing major histocompatibility loci class II antigens. These activation proteins are characteristic of T-lymphocytes and macrophages and are involved in the receptor transmission of immune information, indicating the ability of SMCs to participate in immune reactions in AS. In addition, smooth muscle cell proliferation may be beneficial throughout atherogenesis, even though smooth muscle cell-derived macrophage-like cells may promote inflammation [10, 12, 17].

The objective: was to determine the interaction of vascular smooth muscle cells with endothelial cells in the process of atherogenesis in the presence of metabolic syndrome.

MATERIALS AND METHODS

To achieve this goal, we carry out a set of clinical and morphological studies.

Sample size: 150 cases.

In the course of works we studied the following groups:

Group I – 50 patients who died as a result of complications associated with cerebral atherosclerosis in the setting of metabolic syndrome,

Group II – 50 patients who died as a result of complications associated with cerebral atherosclerosis without a history metabolic syndrome,

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Group III (comparison group) – 50 patients who died from causes unrelated to MS and AS.

We studied the carotid and extracerebral arteries, demacroscopically detected atherosclerotic changes in the vessel walls, and in the comparison group we studied unaffected areas of the vessels.

The following histological and histochemical methods were used for the study: haematoxylin-eosin, Masson's method, Van Gieson's method, Weigert's method, and immunohistochemical examination using monoclonal antibodies. For the identification of smooth muscle cells: immunocytochemical markers – Actin Smooth Muscle Ab-1 (Clone 1A4), Vimentin Ab-2 (CloneV9), Desmin (Muscle Cell Marker Ab-1 CloneD33), immunocompetent cells – CD4 (CD4 Ab-8), CD8 (SP-16), CD20 (CD20 Ab-1), CD68 (CD68/Macrophage Marker Ab-4) and immunocytochemical marker – CD31/PECAM-1 (Endothelial Cell Marker) Ab-1 to determine the endothelium state.

The results of immunohistochemical reactions of immunocompetent cell markers CD4 (T-helper), CD8 (T-suppressor), CD20 (B-lymphocyte) and CD68 (macrophage) were evaluated under a microscope at 400 magnification by counting positively stained cells in 10 randomly selected fields of view. The results of immunohistochemical reactions of mesenchymal cells markers and their derivatives, smooth muscle cells, fibroblasts and endothelial cells were evaluated as the specific volume of positively stained cells per unit area.

The results of immunohistochemical reactions were evaluated by the semi-quantitative method in points from 0 to 6 according to the generally accepted method, taking into account stained cells, where 0 points – no staining, 1 point – up to 10% staining, 2 points – up to 20%, 3 points – up to 30%, 4 points – up to 40%, 5 points – up to 50%, 6 points – more than 50% cell staining. The degree of staining intensity was also assessed, where 0 is no staining, 1 (+) is a weak light brown staining, 2 (++) is a moderate brown staining, and 3 (+++) is a pronounced dark brown staining. Histological examination and microsections' photography were performed using an AxioScop 40 microscope (Zeiss).

Blood vessels contain two main types of cells: endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). Each of them performs an important function in maintaining vascular homeostasis. EC-VSMC communication is important not only for the development but also for the homeostasis of mature blood vessels, and their abnormal interaction can contribute to atherogenesis.

In the study groups with atherosclerosis manifestations, we observed manifestations in the form of lipid spots, fibrous plaques, calcification, stenosis, and obliteration.

The most pronounced changes were observed in the areas of functional vascular load – arterial bifurcation. There was a predominance of stenotic and obliterating variants of the main vessels lesions, with inner lining hyperplasia with diffuse-focal lymphocyte-macrophage infiltration (Fig. 1).

In areas of intimae proliferation on the periphery of atheromatous detritus, we detected macrophages with lipid inclusions (xanthoma cells) with foamy cytoplasm and round nucleus and (Fig. 2).
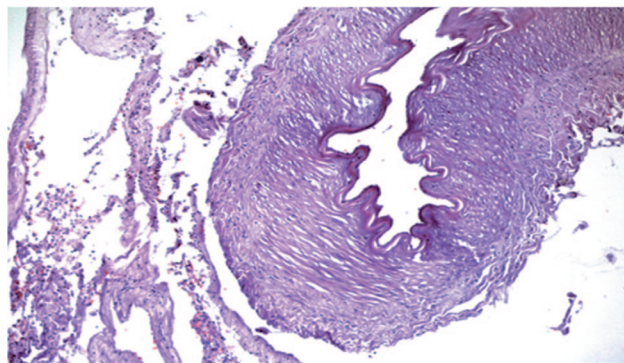
Fig. 1. Significant thickening of the arterial wall with lumen stenosing. Staining: hematoxylin-eosin, × 200
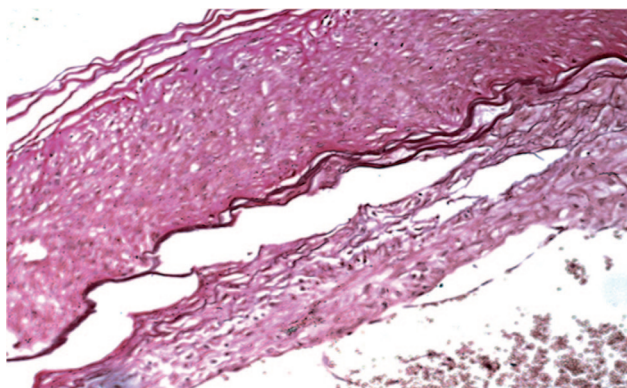(Source: Author)
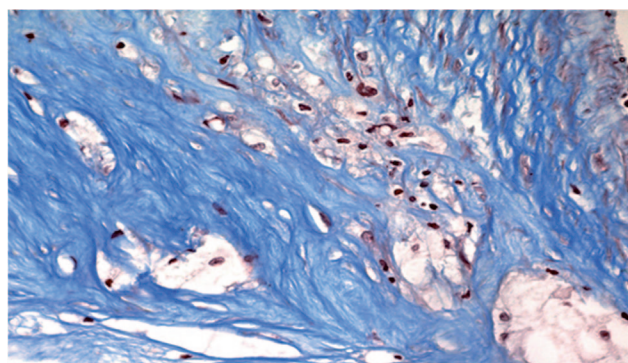
Fig. 2. Xanthoma cells in fibro-lipid plaque of an artery. Staining: Masson's trichrome, × 200
(Source: Author)

In the majority of arteries, wall thickening was associated with proliferation of connective tissue fibres, mainly collagen fibres. Collagen fibres proliferation led to arteries inner coat thickening, causing a significant narrowing of their lumen. Intimae smooth muscle cells intensively manifest their metabolic functions by absorbing modified lipoproteins. Alongside with lipid accumulation in foam cells and connective tissue proliferation, we observed dystrophic changes in elastic fibres, including the inner elastic membrane. The inner elastic membrane became thinner and thus facilitated lipids penetration into the middle membrane (Fig. 3).

It should be noted that arterial perfusion decrease is not only due to widespread atherosclerotic lesions of the main arteries and basilar arteries; structural changes in small intracerebral arteries are also a manifestation of microangiopathy in diabetes mellitus, which is the metabolic syndrome component.

The development of atherosclerotic lesions was characterised by migration of smooth muscle cells into intimae and their proliferation. In many cases, it was observed that the collagen fibres growth reached significant sizes, with the lumen of the vessels being completely obliterated by fibrous hyalinised tissue without elastic fibres (Fig. 4).

Arterial smooth muscle cells (SMCs) are estimated to account for >90% of all human atherosclerotic plaque cells and are present in the pre-atherosclerotic arterial intimae starting in utero [11, 12].

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Fig. 3. Thickening of the arterial wall due to collagen fibre proliferation. Atheromatous masses deposition on the internal elastic membrane of the artery. Staining: van Gieson's picrofuchsin, Weigert's resorcinol-fuchsin, ×200
(Source: Author)
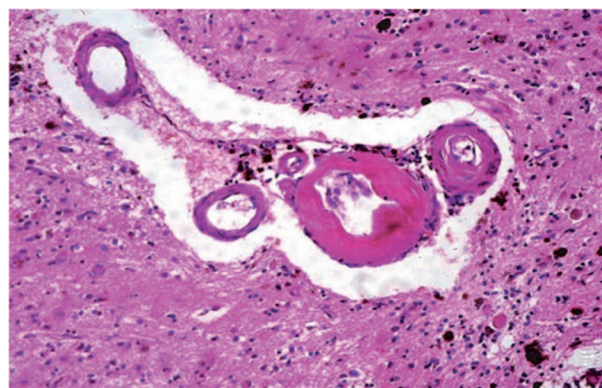
Fig. 4. Cerebral artery hyalinosis. Staining: haematoxylin-eosin, ×400
(Source: Author)

The immunohistochemical reaction with vimentin revealed the presence of connective tissue components, severe fibrosis of the arterial wall, fibrous plaques of various sizes and shapes, from small segmental to circular, and sometimes multiple, which contributed to the vascular wall sclerosis (Fig. 5).

The expression of vimentin in the wall of atherosclerotic affected arteries of the study Group I constituted 57.6±3.9% (p>0.05) to the total area; in the study Group II – 52.9±2.4% (p>0.05) and in the comparison group the expression of vimentin constituted 50.8±7.1 (p>0.05).

In many cases, we noted the formation of longitudinal folds of the vessel wall protruding into the vessel lumen and half-narrowing it, significant changes in the muscle layer in the form of thickening and stratification, and intense expression of vimentin. There was a sharp tortuosity of the inner elastic membrane. It is vimentin that ensures the strength of cells and their resistance to mechanical stress [12, 14]. Vimentin expression showed that vascular wall fibrosis increases with the progression of the underlying disease, i.e. MS.

The changes in the inner elastic membrane consisted in stratification, loosening and increase of its tortuosity. The most significant changes were observed in the edge of the inner elastic membrane on the intimae side, while the edge adjacent to the middle membrane was preserved.

Intense expression of alpha-actin was observed in the intimae and media cells. In the study Group I it constituted 64.1±5.4% (p>0.05), in the study Group II – 56.7±3.9% (p>0.05) (Fig. 6). In the comparison group the expression constituted 53.9±6.1% (p>0.05).

However, in some areas, complete lysis of the inner elastic membrane was observed, which led to intense lipid penetration.
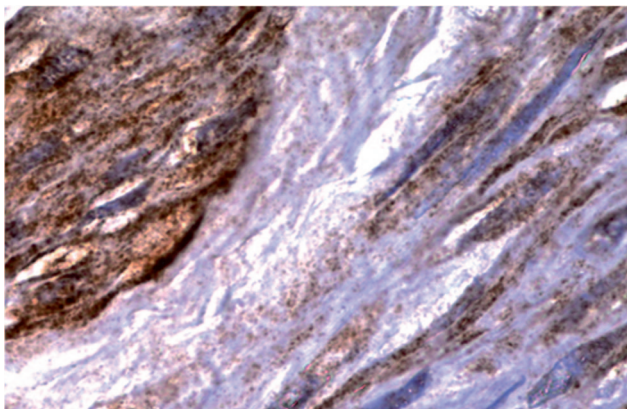
We found desmin deposition in the smooth muscle cells of the inner coating and its absence in the intimae cells (Fig. 7). We also noted intimae thickening with the fibrous plaque formation, which was due to the smooth muscle cells proliferation and connective tissue elements hyperproduction.
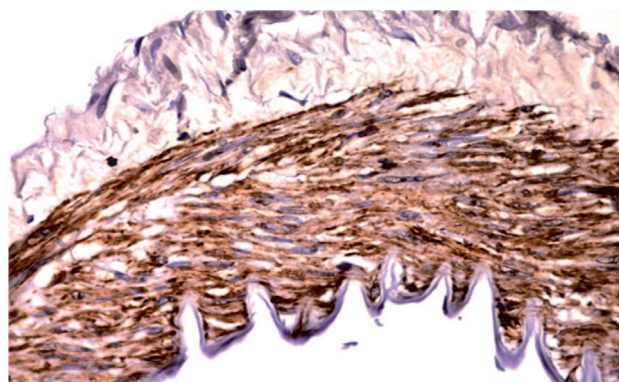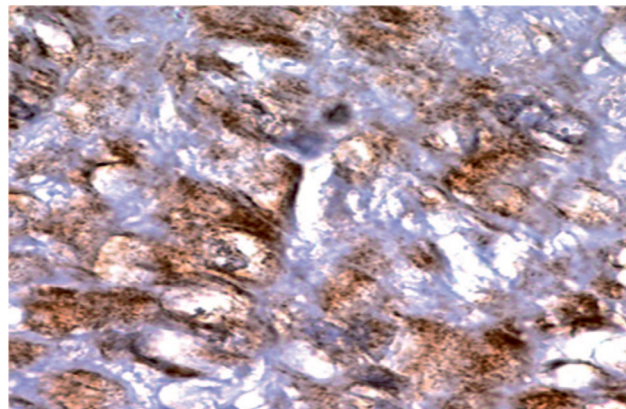

Fig. 5. Intense expression of the Vimentin Ab-2 marker in the arterial wall Staining: immunohistochemical technique with primary antibodies of Vimentin Ab-2 positive cells, × 200
(Source: Author)
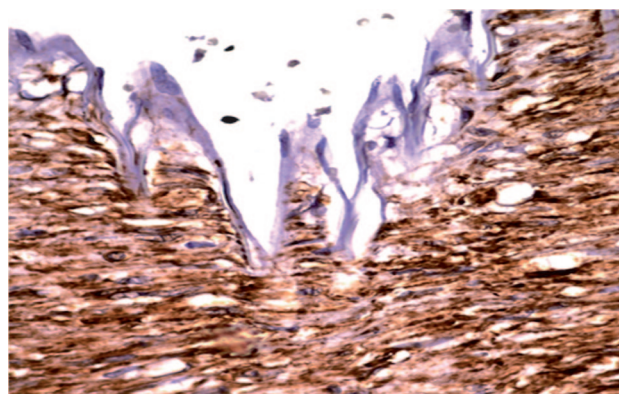
Fig. 6. Intense expression of Actin Smooth Muscle Ab-1 marker in the arterial wall with metabolic syndrome manifestations. Staining: immunohistochemical technique with primary antibodies of Actin Smooth Muscle Ab-1 positive cells, × 200
(Source: Author)

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Fig. 7. Expression of Desmin marker in the arterial wall. Staining: immunohistochemical technique with primary antibodies of Desmin positive cells. ×400
(Source: Author)

Fig. 8. Intense expression of the CD68 marker in the arterial wall. Staining: immunohistochemical technique with primary antibodies of CD68 positive cells, ×400
(Source: Author)

In quantitative terms, in the group of patients with MS, the desmin expression constituted 15.1±4.2% (p>0.05); in the study Group II, the expression constituted 13.5±2.9% (p>0.05).

The initial link in autoimmune reactions occurring in the vascular wall in atherosclerosis is the formation of modified low-density lipoprotein (LDLs) under the influence of various factors [2, 3, 15]. Modified LDLs activate cells of haematogenous origin – monocytes, macrophages, lymphocytes that migrate to the arterial intimae, and vascular wall cells – endothelial cells, stellate cells and smooth muscle cells, which cause reactions that maintain the focus of inflammation in the arterial wall [7, 9, 23].

A significant number of CD68 positive cells with marker expression in the cytoplasm was noted in the areas of atheromatous changes (Fig. 8). In the study group with MS manifestations, the expression constituted 18.92±1.37 (p>0.05), in the group without MS manifestations, the expression constituted 15.73±1.36 (p>0.05). In the comparison group, the number of CD68 positive cells constituted 6.49±1.57 (p>0.05).

We detected accumulation of blood monocytes in the damaged endothelial layer and subendothelial space, followed by their transformation into macrophages, lipid uptake; the cytoplasm became foamy, i.e. foamy cells were formed. However, recent studies have shown that 40% of foam cells in common human coronary artery lesions express both the SMCs alpha-actin marker and the macrophage CD68 marker, although it is unclear whether these are SMC-derived cells with activated macrophage markers or macrophages with activated SMC markers (Allahverdian et al., 2014). A number of studies have shown that smooth muscle cells actively expressing major histocompatibility complex class II antigens are found in atherosclerotic vascular plaques.

These activation proteins are characteristic of T-lymphocytes and macrophages and are involved in the receptor transmission of immune information, indicating the ability of SMCs to participate in immune reactions in AS [8, 11, 12, 21].
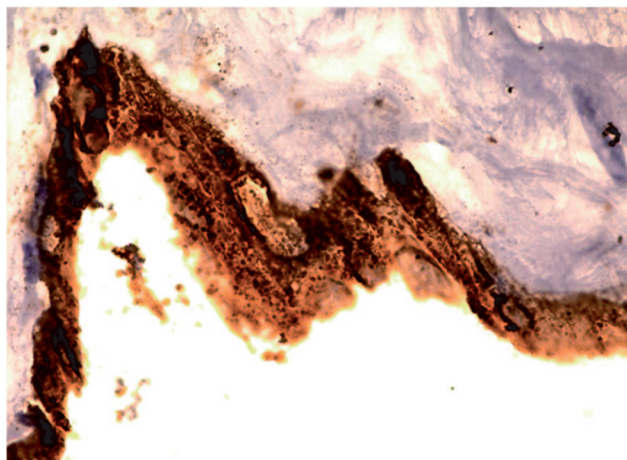
The inflammatory nature of the process is evidenced by the presence of T-lymphocytes and focal infiltration with macrophages in areas of atheromatous changes.
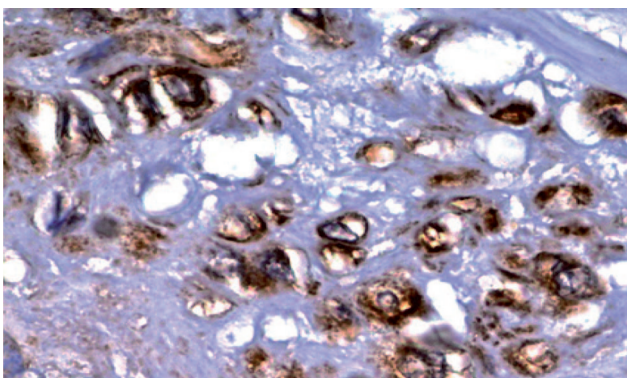
Fig. 9. Intense expression of CD4 marker in the arterial wall. Staining: immunohistochemical technique with primary antibodies of CD4 positive cells, ×400
(Source: Author)
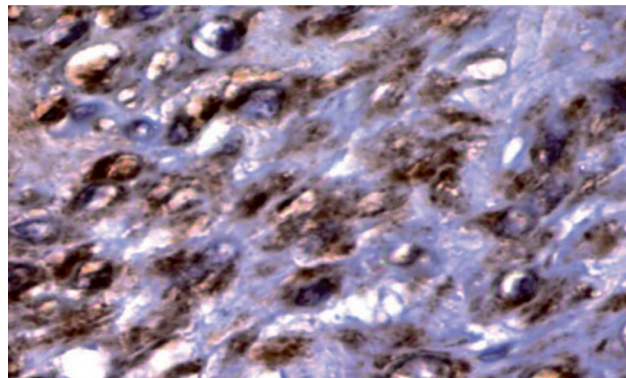
Fig. 10. Intense expression of CD8 marker in the arterial wall. Staining: immunohistochemical technique with primary antibodies of CD8 positive cells, ×400
(Source: Author)

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Fig. 11. Intense expression of CD31 marker in the arterial endothelium of a patient with atherosclerosis in the settings of metabolic syndrome. Staining: immunohistochemical technique with primary antibodies of CD31 positive cells, × 400
(Source: Author)

In the areas of atherosclerotic lesions formation, CD4 positive cells were observed – helper T-lymphocytes, whose expression constituted 13.15±1.26 (p>0.05) in Group I and 11.43±1.27 (p>0.05) in Group II (Fig. 9). The expression of the CD8 marker in T suppressor lymphocytes constituted 7.93±1.17 (p>0.05) and 8.11±1.36 (p>0.05), respectively, in the study groups (Fig. 10).

Abnormal heterotypic cell communication can cause vascular defects. The main evidence supporting this notion is that endothelial dysfunction, a well-defined pathological state of the endothelium, underlies vascular disorders in atherosclerosis, hypertension, hypercholesterolaemia and diabetes [3, 5, 7]. The endothelium of the cerebral vessels in AS acquires structural changes. In many cases, it was noted that the endothelial cells were sharply elongated, the cell thickness was very small, and the nuclei were flattened. In the vessels lumen, there was an accumulation of desquamated apoptotic endothelial cells, as indicated by their intense expression (Fig. 11).

Immunopositivity of the CD31 marker was observed in the cytoplasm and cell membrane In the study GroupI we detected uneven deposition of antigen in the endothelium – 3.7±0.2 (p>0.05) points.

Immunohistochemical studies have shown that there is a close relationship between structural changes in endothelial cells and intimae damage. The endothelium functions are aimed at regulating permeability and adapting to the triggering factors effects. The CD31 marker immunopositivity in the arterial walls ranged from moderate with uneven antigen deposition to focal high immunopositivity, which was combined with its complete absence in large areas.

Under physiological conditions, the endothelium has low proliferative activity, mainly due to its own elements through amitotic division of endothelial cells. It is capable of maintaining the continuity of the cell layer through intact cells migration and division [7, 11,

20, 22]. Thus, de-endothelialisation caused by a pathological condition triggers the process of reparative regeneration and violation of this process, most often in atherogenesis, leads to pathological regeneration, when in de-endothelialised areas of the vascular wall, proliferation of subordinate smooth muscle cells occurs with the formation of myointimal thickenings – atheroma predecessors [20, 21, 23].

Thus, the complex structure of an atherosclerotic plaque reflects the complex cellular and extracellular environment, as well as the close interconnection between all cellular components of the vascular wall. It has been determined that the VSMCs role is an additive effect of these processes and may change during atherogenesis, and inhibition of changes in the SMC phenotype may be useful in advanced atherosclerosis.

These results may become a therapeutic target for more effective clinical treatment of atherosclerosis as a structural basis of cerebral arterial lesions in MS. An important goal for future research is to identify factors and mechanisms that may contribute to beneficial changes in the SMCs phenotype and processes that can either enhance or replace antiatherosclerotic therapy, which is currently not effective enough.

CONCLUSIONS

1. Intensive immunohistochemical reaction of the Desmin marker in the arterial wall indicates the ability of phenotypic transformation of SMCs, which is an important feature of the underlying disease and a decisive link of atherosclerosis pathogenesis.

2. The presence of lymphocytes in the atherosclerotic process involves interaction with macrophages, endothelial cells and SMCs. Lymphocytes potentiate the activation of macrophages and SMCs in the foci of atheromatous changes and subsequent atheromatous plaque formation through cellular and humoral immune responses.

3. A decrease in the number of endothelial progenitor cells, which are actively involved in endothelial regeneration, contributes to the development of atherosclerosis. The severity of endothelial dysfunction is of prognostic significance for atherogenesis.

4. Changes in the phenotype of arterial intimae SMCs are accompanied by increased proliferation and synthesis of collagen, elastin, and glycosaminoglycans, and modified SMCs are responsible for the formation of the plaques fibrous base.

5. The lipid-enriched and inflammatory environment of plaques induces phenotypic switching of SMCs to both beneficial and harmful phenotypes. Macrophage heterogeneity increases with disease severity to a variety of proinflammatory and anti-inflammatory activation states. These vascular cell phenotypes are determinants of plaque structure stability.

6. There is no significant difference in the infiltration of the vascular wall with immunocompetent cells in terms of their number and nature depending on the manifestations of MS, which indicates that vascular changes morphogenesis is determined by the underlying disease.

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